Remarks

Claims 68-71, 77 and 96-103 stand rejected for alleged lack of enablement. The Examiner states that applicants are enabled for the zinc finger proteins listed in Tables 3 and 4 that bind to a VEGF gene. However, the Examiner alleges it is unclear if all the ZFPs will bind to the VEGF-A gene. The Examiner also alleges lack of clarity as to with which species of VEGF ZFPs will interact. The Examiner also says that published literature indicates that zinc-finger DNA binding proteins achieve single-gene specificity. The Examiner also says there is a lack of working examples.

Applicants understand that the Examiner's position is that the claims are enabled for the zinc finger proteins listed in Tables 3 and 4 but not other zinc finger proteins. Insofar as applicants have correctly understood the rejection, it is respectfully traversed for the following reasons. If applicants understanding of the rejection is incorrect, further clarification is requested in the next office action.

The specification provides both working examples and considerable guidance for designing ZFPs that bind to the claimed target sites and modulate VEGF genes. Tables 3 and 4 describe almost 40 examples of ZFPs (and their target sites) suitable for use in the claimed methods. The specification also provides general teaching and examples of how a ZFP can be linked to an activation or repression domain to activate or repress expression of a target gene (see, e.g., paragraph bridging pp. 28-29). The specification also provides general teaching and examples illustrating modulation of a target gene both in cells (see, e.g., pp. 80-83, and 87-88) and animals (see pp. 85-86 and 88-100).

The specification also provides considerable guidance for design or selection of ZFPs capable of binding to any desired target site (see pp. 40-42). The methods include rational design using rules correlating amino acids occupying certain positions in a ZFP with nucleotides occupying a target site, and phage display in which a randomized library of ZFPs is affinity selected, using the desired target site for selection. No reason has been identified why such approaches would not be expected to identify additional ZFPs beyond the almost 40 already identified.

The Examiner's concern regarding whether ZFPs bind to the VEGF-A gene is unwarranted. Table 2 shows that all of the target sites shown in Tables 3 and 4 occur within the VEGF-A gene. Accordingly, any zinc finger designed to bind to a target site in Table 3 or 4 will bind to the VEGF-A gene. Some of the target sites shown in Tables 3 and 4 also occur in other VEGF genes, such as VEGF-B, VEGF-C and so forth, as shown in Table 2. Thus, based on the teaching of the specification a user can readily select a zinc finger protein that is specific to VEGF-A, or binds to VEGF-A and one or more other VEGF-genes.

Moreover, the K_d values shown in Table 3 are within the range (low nanomolar to high picomolar) characteristic of specific binding of a zinc finger to its target site.

Similar considerations apply with regard to VEGF genes from different species. One can determine whether a particular ZFP binds to a particular VEGF gene simply by inspecting whether the sequence of the gene includes the target site of the ZFP. Because there are some segments of sequence identity and some regions of divergence between VEGF genes from different species, some target sites (and ZFPs binding to the target sites) will be species specific, whereas others will bind to corresponding VEGF genes from multiple species. Again, the user can readily select a ZFP having a desired species specificity simply by comparing the target site of the ZFP with the sequence of the VEGF gene from the desired species.

The Examiner's comment that the prior art teaches that ZFPs achieve single gene specificity is partly correct but not detrimental to enablement of the claimed methods. If a single gene contains a unique target site, then a ZFP targeted to that site can be designed to bind specifically only to that site. If, however, the gene is part of a family, and other genes in the family share the target site, then a ZFP can be designed to bind to each member of the family containing the target site (as for the ZFP's described at p. 87, lines 25-30 of the specification). In any event, the user can readily select a ZFP that binds to one member of the VEGF family or binds to multiple members depending on the target site of the ZFP, as discussed above.

In view of the numerous examples of ZFPs suitable for practice of the claimed methods, and general guidance as to producing others provided by the specification, it is respectfully submitted that the claims are enabled for their full scope, and the rejection should be withdrawn.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at .

Respectfully submitted,

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